IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 10/518,814	Confirmation No.	: 8244
First Named Inventor	: Isao SAKATA		
Filed	: December 23, 2004		
TC/A.U.	: 1617		
Examiner	: Sahar JAVANMARD		
Docket No.	: 101512.55677US		
Customer No.	: 23911		
Title	: Method of Photodynamic Diagnosis for Vascular Diseases		

APPEAL BRIEF

Mail Stop Appeal Brief- Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

On November 26, 2008, Appellants appealed to the Board of Patent Appeals from the final rejection of claims 1-2, 7-8, and 13-14. Accordingly, the following is Appellants' Appeal Brief submitted pursuant to 37 C.F.R. § 1.192.

I. REAL PARTY IN INTEREST

The real party in interest in this Appeal is the assignee of record, Hamamatsu Photonics K. K., a Japanese Company having an address at: 1126-1, Ichino-cho, Hamamatsu-shi, Shizuoko, Japan, as reflected in the assignment appearing at Reel/Frame 016650/0054.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals and interferences.

III. STATUS OF CLAIMS

Claims 1-2, 7-8, and 13-14 are currently pending in this application. All of these claims stand rejected, and all of these rejections are being appealed. Accordingly, the following is a statement of the status of all claims in this proceeding:

Claim 1. Rejected, and being appealed.

Claim 2. Rejected, and being appealed.

Claim 3. Cancelled.

Claim 4. Cancelled.

Claim 5. Cancelled.

Claim 6. Cancelled.

Claim 7. Rejected, and being appealed.

Claim 8. Rejected, and being appealed.

Claim 9. Cancelled.

Claim 10. Cancelled.

Claim 11. Cancelled.

Claim 12. Cancelled.

Claim 13. Rejected, and being appealed.

Claim 14. Rejected, and being appealed.

Claim 15. Cancelled.

Claim 16. Cancelled.

Claim 17. Cancelled.

Claim 18. Cancelled.

Claims 3-6, 9-12 and 15-18 were previously cancelled and are not being appealed. Appellant hereby seeks reversal of the final rejection of Claims 1-2, 7-8, and 13-14.

IV. STATUS OF AMENDMENTS

There have been two Office Actions issued in this matter.

A first Office Action was issued by the Examiner on September 27, 2007, rejecting claims 1-18. In an amendment submitted on February 26, 2008, Appellants amended claims 1, 7, and 13, and canceled claims 3-6, 9-12, and 15-18. This amendment has been entered. A final Office Action was subsequently

issued by the Office on May 25, 2008. No amendments have been submitted subsequent to the Final Office Action and there are no un-entered amendments.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 is directed to a method for treating rheumatoid arthritis by photodynamic therapy with a particular iminochlorine aspartic acid derivative. The iminochlorine aspartic acid derivative formulation used in this method is described in the specification, for instance, on page 2, beginning on line 1 and continuing to line 10. The method according to this claim is described in the specification, for instance, on page 10, line 9 through line 26 of page 13.

Independent claim 7 is directed to a method for treating inflammatory keratosis by photodynamic therapy. The iminochlorine aspartic acid derivative formulation used in this method is described in the specification, for instance, on page 2, beginning on line 1 and continuing to line 10. The method according to this claim is described in the specification, for instance, on page 13, beginning on line 28 through line 13 of page 16.

Independent claim 13 is directed to a method for determining the location of a sentinel lymph node and the presence of cancer metastasis by photodynamic therapy and detecting fluorescence with a fluorescent imaging system. The iminochlorine aspartic acid derivative formulation used in this method is described in the specification, for instance, on page 2, beginning on line 1 and continuing to line 10. The method according to this claim is described in the

specification, for instance, on page 16, beginning on line 15 through line 17 of page 19.

In compliance with the second sentence of 37 C.F.R. § 41.37(c)(1), Appellants note that none of the claims involved in the appeal contain any means plus function or step plus function limitations within the meaning of 35 U.S.C. § 112, sixth paragraph.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection to be reviewed on appeal are:

(i) whether claims 13 and 14 are obvious under 35 U.S.C. § 103(a) over Hikida et al., (US 6,063,777);

(ii) whether claims 1-2 and 7-8 are obvious under 35 U.S.C. § 103(a), over Hikida et al., (US 6,063,777) in view of Levy (Trends Biotechnology, 1995).

VII. ARGUMENT

A. Claims 13 and 14 Are Not Obvious Over Hikida et al., Under 35 U.S.C. § 103(a).

Claim 13 is directed to a method for determining the location of a sentinel lymph node and the presence of cancer metastasis by photodynamic therapy. The method involves the steps of administering an iminochlorine aspartic acid derivative of formula (I) or a pharmaceutically acceptable salt thereof and then

detecting fluorescence with a fluorescent imaging system. Claim 14 adds that the salt of claim 13 is a sodium salt.

The Office Action of May 28, 2008 correctly acknowledges that Hikida does not teach the use of the iminochlorine aspartic acid derivative of the compound of formula (I) of the present invention for determining the location of a sentinel lymph node and the presence of cancer metastasis by photodynamic therapy (PDT), see page 4 of the Office Action.

Despite this, the Office Action concludes that based on Hikida, one of ordinary skill in the art would expect that the administration of the compound (I) of the present invention would be successful in detecting the sentinel lymph node, and, as a result, detecting the presence of metastasis. In particular, the third page of the Advisory Action mailed December 23, 2008 (marked as page 2) states that Hikida teaches the instant compound is useful as a diagnostic agent and a treatment agent for cancers and for ophthalmic vascularization. From this, the Examiner concludes that it would have been obvious to use the compound in "determining the location of various cancers, namely the sentinel lymph node." Thus, determining the location of cancers appears to be equated with determining the location of the sentinel lymph node. The two are not the same, however, and a teaching of the former does not necessarily mean that there is a teaching of the latter. Further, determining the location of cancers is not the same as determining the presence of cancer metastasis.

Review of Hikida reveals that it does not mention any of the following words: sentinel, lymph, node, and metastasis. Although the reference indicates

that the compounds described therein might be useful for diagnosing cancer, based on the accumulability of the compound in cancer cells and the rapid excretion from normal cells, there is no indication anywhere in the reference that the compounds would accumulate in the sentinel lymph node. Further, there is no indication that aggregation of the compounds in the sentinel lymph node might be at all indicative of metastasis. The Office Action states that because the reference indicates the compounds would be useful as diagnostic agents, there would be an expectation that the compounds would be useful to detect the sentinel lymph node.

However, there is no explanation, on the present record, of why these diagnostic agents of the reference would be useful to detect the sentinel lymph node and the presence of cancer metastasis. In particular, the record lacks any explanation as to how or why the skilled artisan would understand Hikida's teachings to render obvious the presently claimed methods. The record does not explain why the skilled artisan would reasonably expect that compounds thought to be useful as a diagnostic agent and a treatment agent for cancers and for ophthalmic vascularization would be useful in methods to detect (i) the location of a sentinel lymph node and (ii) the presence of cancer metastasis.

The ability to reliably detect the sentinel lymph node and the presence of cancer metastasis is of great significance in combating various cancers. It is widely known that early detection of cancer can be of paramount importance in the clinical outcome for a patient. It is also of great importance to be able to measure the progress of a given cancer. These techniques at issue in the present

application provide a treating physician with a new tool to determine whether cancer has metastasized to the sentinel lymph node. The cited prior art refernce does not teach a method to perform these operations.

Absent some teaching or suggestion that these compounds would be useful to determine the location of a sentinel lymph node and to determine the presence of cancer metastasis, the cited reference fails to describe the claimed method and cannot, therefore, render the claimed methods obvious. The record includes no complete reasoned explanation as to what would lead the skilled artisan to depart from the teachings of the reference and then arrive at the invention of claims 13 and 14.

As pointed out by the Supreme Court in KSR International Co. v. Teleflex Inc., 127 SCt 1727, 82 USPQ2d 1385, 1396 (U.S. 2007):

> [R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness". (Quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329 (Fed. Cir. 2006) with approval).

Thus, to properly reject for obviousness, it is nevertheless necessary for the Examiner to articulate a convincing rationale as to what would lead a person skilled in the art to depart from the teachings of the prior art and strike out in the new direction claimed by applicants as their invention. Because the recent Office Action does nothing more than simply restate the invention of claims 13 and 14 and then conclude that this method would have been obvious, it follows that a proper, *prima facie* case of obviousness has not been made out, and the rejection should be withdrawn.

Accordingly, the Board is respectfully requested to reverse this rejection.

B. Claims 1, 2, 7, and 8 Are Not Obvious Under 35 U.S.C. § 103(a), over Hikida et al., (US 6,063,777) in view of Levy (Trends Biotechnology, 1995).

Claims 1 and 2 are directed to a method for treating rheumatoid arthritis by photodynamic therapy. The method involves administering an iminochlorine aspartic acid derivative according to formula (I) or a pharmaceutically acceptable salt thereof. Claim 2 adds that the aspartic acid derivative is in the form of a sodium salt.

Similarly, claims 7 and 8 are directed to a method for treating inflammatory keratosis by photodynamic therapy. The method involves administering an iminochlorine aspartic acid derivative according to formula (I) or a pharmaceutically acceptable salt thereof. Claim 8 adds that the aspartic acid derivative is in the form of a sodium salt.

The Advisory Action of May 28, 2008 acknowledges that Hikida does not explicitly teach the use of an iminochlorine aspartic acid derivative according to compound (I) of the present invention for treating of rheumatoid arthritis or inflammatory keratosis, see the third page of the Advisory Action mailed (marked as page 2).

The Examiner offers Levy as teaching that photodynamic therapy may have efficacy for psoriasis and autoimmune conditions, among other disorders. The Office Action equate psoriasis with inflammatory keratosis. However, psoriasis is but one of a number of conditions falling within the classification "inflammatory keratosis". In addition to psoriasis, "inflammatory keratosis"

includes various forms of dermatitis and eczema, the broad class of papulosquamous disorders (of which psoriasis is but one among many), as well as the urticaria and erythema disorders. There is nothing in Levy which even suggests that the photodynamic therapy would be effective for treating all of the numerous and varied conditions falling within the classification "inflammatory keratosis". Accordingly, the skilled artisan would have no reason to modify the teachings of Levy so as to encompass treating inflammatory keratosis rather than psoriasis.

Further, Levy only discloses the potential indications for PDT, and there is no description of the actual treatments for these diseases using photosensitizers such as the compound of formula I of the present invention. Levy only teaches the possibility of PDT therapy for these diseases. Moreover, the compound of formula I of the present invention is not suggested or described in Levy.

The skilled artisan would not be inclined to modify the teachings of Hikida based on the speculative assertions in Levy. Given that Levy provides no test results or clinical data showing the efficacy of the compounds described therein to treat the presently claimed conditions, the skilled artisan would not simply accept that the proposed treatment methods suggested by Levy would actually work in a clinical setting.

Further, the reference teaches that some photosensitizers have undesireable properties, for instance a photosensitizer may have an activation wavelength of light that is too low, thereby preventing adequate light penetration and limiting the size and depth of tumors that could be effectively

treated. Other issues associated with known photosensitizers include the clearance rate of the compound, a clearance rate that is too slow may render a patient too sensitive to light exposure and for instance, preclude a patient from being exposed to sunlight. A clearance rate that is too fast could preclude adequate accumulation of the photosensitizer, thereby rendering any treatment attempts unsuccessful. Still further, the rate and degree to which the compound selectively accumulates in tumors is important and certain minimum thresholds must be met before a compound can be suitable for photodynamic therapy.

Thus, the Levy reference actually suggests to the skilled artisan that not all photosensitizers are suitable for all photodynamic therapies. Still further, the broader implications of Levy's teaching that photosensitizer molecules will accumulate selectively in abnormal or hyperproliferative cells, that is, rapidly dividing or activated cells and neovasculature, suggests to the skilled artisan that the photosensitizer might accumulate in a wide variety of cells, thereby rendering photodynamic therapy unhelpful, or even dangerous, as in the case where the photosensitizer accumulates in cells where its effects are undesirable. Indeed, increasing photosensitivity in an organism is generally considered an adverse effect for many pharmaceutical compounds.

As such, not only would the skilled artisan not consider Levy to adequately teach a method of treating rheumatoid arthritis or inflammatory keratosis with photodynamic therapy, because the statements in Levy are speculative, the skilled artisan would not be inclined to try to substitute the photosensitizers described in the reference with other potential sensitizers.

Accordingly, the proposed combination of references would not cause the skilled artisan to arrive at the invention of the present claims. As a result, the Office Action has not made out a proper showing of obviousness for the claimed methods of treatment. The Office Action's pointing to a reference which states that a claimed compound is a photosensitizer and then relying on a second reference which makes an unsubstantiated assertion that the claimed conditions are "potential indications for PDT", *see* Table 1 on page 16 of Levy, does not amount to a proper showing of obviousness.

The pending claims are directed to new methods of treatment. At best, the art suggests that other, significantly different, compounds *might* be suitable to treat the claimed conditions. However, the gap between the conjecture set forth in Levy and the kind of teaching that leads to a reasonable expectation of success is too great to allow the assertion of obviousness based on Levy to stand.

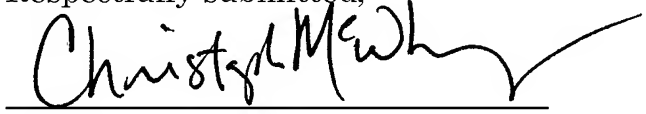
Accordingly, the Board is respectfully requested to reverse this rejection.

VIII. CONCLUSION

For the foregoing reasons it is respectfully submitted that the rejections of Appellant's claims 1-2, 7-8, and 13-14, are improper, and therefore, these grounds of rejection should be reversed.

An extension of the deadline for filing this Appeal Brief is respectfully requested and the appropriate fee is submitted herewith. This Appeal Brief is being submitted with the required fee of $540.00. This amount is believed to be correct, however, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 05-1323, Docket No.: 101512.55677US.

Respectfully submitted,



March 26, 2009

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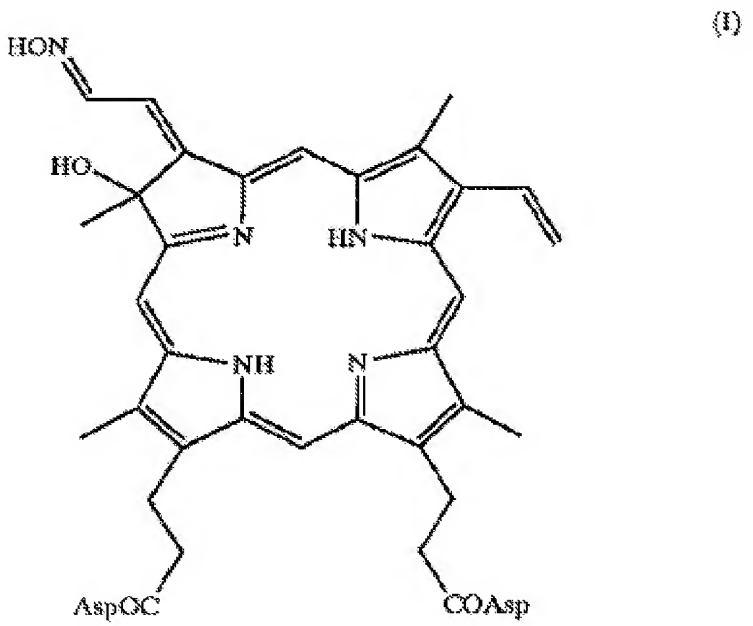
CLAIMS APPENDIX

1. A method for treating rheumatoid arthritis by photodynamic therapy, comprising administering an iminochlorine aspartic acid derivative of the following formula (I):

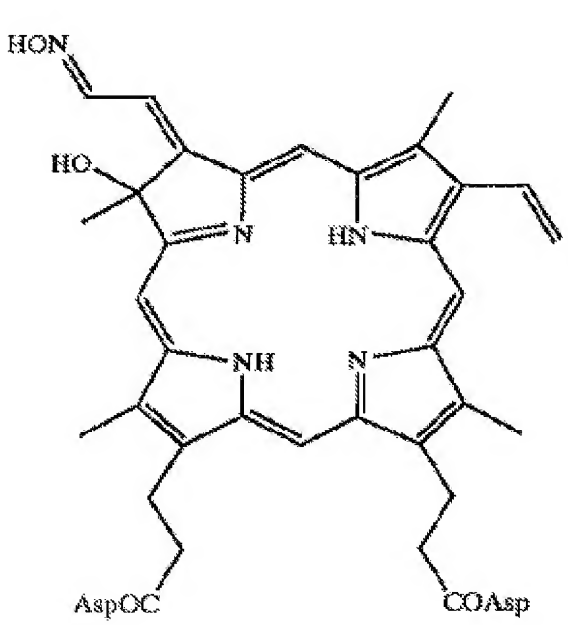


wherein asp represents aspartic acid residue; or a pharmaceutically acceptable salt thereof.

2. The method according to claim 1, wherein the iminochlorine aspartic acid derivative of the formula (I) or a pharmaceutically acceptable salt thereof is a sodium salt.

7. A method for treating inflammatory keratosis by photodynamic therapy,

comprising administering an iminochlorine aspartic acid derivative of the following formula (I)



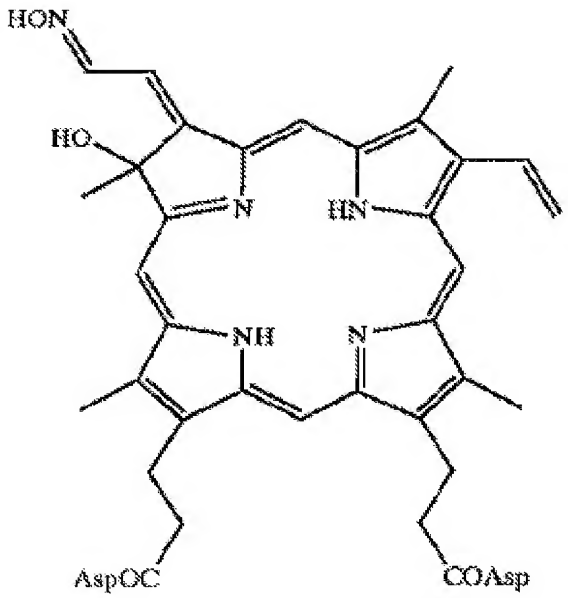
(I)

or a pharmaceutically acceptable salt thereof.

8. The method according to claim 7, wherein the iminochlorine aspartic acid derivative of the formula (I) or a pharmaceutically acceptable salt thereof is a sodium salt.

13. A method for determining the location of a sentinel lymph node and the presence of cancer metastasis by photodynamic therapy, comprising administering an iminochlorine aspartic acid derivative of the following formula (I)

(I)



or a pharmaceutically acceptable salt thereof

and detecting fluorescence with a fluorescent imaging system.

14. The method according to claim 13, wherein the iminochlorine aspartic acid derivative of the formula (I) or a pharmaceutically acceptable salt thereof is a sodium salt.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.